



University of Groningen

Rehabilitation, optimized nutritional care and boosting host internal milieu to improve long-term treatment outcomes in TB patients

Akkerman, Onno W; Ter Beek, Lies; Centis, Rosella; Maeurer, Markus; Visca, Dina; Muñoz-Torrico, Marcela; Tiberi, Simon; Migliori, Giovanni Battista

Published in:

International Journal of Infectious Diseases

DOI:

[10.1016/j.ijid.2020.01.029](https://doi.org/10.1016/j.ijid.2020.01.029)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version

Publisher's PDF, also known as Version of record

Publication date:

2020

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Akkerman, O. W., Ter Beek, L., Centis, R., Maeurer, M., Visca, D., Muñoz-Torrico, M., ... Migliori, G. B. (2020). Rehabilitation, optimized nutritional care and boosting host internal milieu to improve long-term treatment outcomes in TB patients. *International Journal of Infectious Diseases*, 92, S10-S14. <https://doi.org/10.1016/j.ijid.2020.01.029>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.



Rehabilitation, optimized nutritional care, and boosting host internal milieu to improve long-term treatment outcomes in tuberculosis patients



Onno W. Akkerman^{a,b}, Lies ter Beek^{a,b}, Rosella Centis^c, Markus Maeurer^d, Dina Visca^{e,f}, Marcela Muñoz-Torrico^g, Simon Tiberi^{h,i}, Giovanni Battista Migliori^{c,*}

^a University of Groningen, University Medical Centre Groningen, Department of Pulmonary Diseases and Tuberculosis, Groningen, The Netherlands

^b University of Groningen, University Medical Centre Groningen, TB Centre Beatrixoord, Haren, The Netherlands

^c Servizio di Epidemiologia Clinica delle Malattie Respiratorie, Istituti Clinici Scientifici Maugeri IRCCS, Tradate, Italy

^d Champamalimaud Foundation, Immunosurgery, Avenida Brasília, Lisbon, Portugal

^e Division of Pulmonary Rehabilitation, Istituti Clinici Scientifici Maugeri, IRCCS, Tradate, Italy

^f Department of Medicine and Surgery, Respiratory Diseases, University of Insubria, Varese-Como, Italy

^g Tuberculosis Clinic, Instituto Nacional De Enfermedades Respiratorias Ismael Cosío Villegas, Ciudad De Mexico, Mexico

^h Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom

ⁱ Department of Infection, Royal London and Newham Hospitals, Barts Health NHS Trust, London, United Kingdom

ARTICLE INFO

Article history:

Received 8 January 2020

Received in revised form 16 January 2020

Accepted 16 January 2020

Keywords:

Tuberculosis

Pulmonary rehabilitation

Disease-related malnutrition

Immune response

ABSTRACT

Background: The holistic management of tuberculosis (TB) patients can improve life expectancy and lost organ function.

Rehabilitation: Chronic sequelae are very common among patients who survive TB, which can lead to a further decline in lung function. There is still no guidance for 'cured' patients with impaired lung function who need pulmonary rehabilitation. Additional tests for evaluation should be given after the end of treatment, as recent studies have shown the good effect of pulmonary rehabilitation for TB patients.

Optimized nutritional care: Malnutrition is very common among TB patients and is related to malabsorption. The latter can cause lower drug exposure, which may result in treatment failure, increasing the risk of death, and can lead to acquired drug resistance. Malnutrition should be assessed according to the Global Leadership Initiative on Malnutrition (GLIM) criteria and the diagnosis should lead to an individualized treatment plan, including sufficient proteins and preferably in combination with adequate training.

Protective immune responses: Under normal circumstances, most immune cells use a glucose-based mechanism to generate energy. Therefore the patient's nutritional status is a key factor in shaping immune responses. Disease-related malnutrition leads to proteolysis and lipolysis. In the end, the identification of individuals who will benefit from immune-modulatory strategies may lead to clinically relevant markers.

© 2020 The Authors. Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Tuberculosis (TB) remains an important cause of mortality globally; however, very little is said of the hundreds of millions of patients who survive the disease. Chronic sequelae are very common, which can range from reduced lung function and post-TB bronchiectasis to aspergilloma and non-tuberculous infections, all of which can further impact lung function. We are only now gaining a better insight into TB as a systemic inflammatory process and understanding that patients are more likely to suffer from vascular events after TB cure. Our ex-TB patients can be expected to be more fragile (Choi et al., 2017a) and are still likely to die 4 years

* Corresponding author at: Servizio di Epidemiologia Clinica delle Malattie Respiratorie, Istituti Clinici Scientifici Maugeri IRCCS, Via Roncaccio 16, Tradate, Varese, 21049, Italy.

E-mail addresses: o.w.akkerman@umcg.nl (O.W. Akkerman), l.ter.beek@umcg.nl (L. ter Beek), rosella.centis@icsmaugeri.it (R. Centis), markus.maeurer@gmail.com (M. Maeurer), dina.visca@icsmaugeri.it (D. Visca), dra_munoz@hotmail.com (M. Muñoz-Torrico), simon.tiberi@bartshealth.nhs.uk (S. Tiberi), giovannibattista.migliori@icsmaugeri.it (G.B. Migliori).

<https://doi.org/10.1016/j.ijid.2020.01.029>

1201-9712/© 2020 The Authors. Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

earlier (Hoger et al., 2014) even though they are cured. The question is, why is this the case and what can be done about it?

The following article discusses the state of the art on the holistic management of TB patients aimed at recuperating lost organ function and raising post-TB life-expectancy, as well as topics for future research in the field. In particular the review is focused on (1) the functional evaluation of TB patients at the end of treatment and rehabilitation of sequelae; (2) optimization of nutritional care, and (3) new insights into the protective immune response.

Methods

A non-systematic review of the literature was conducted by the members of the writing committee, so as to include useful core references that may help the reader better understand the topics covered. The following keywords were used, without any time limitation: 'tuberculosis', 'functional evaluation', 'pulmonary rehabilitation', 'nutrition', 'protective immune response'. MEDLINE was used as the search engine, focusing on the English-language literature only.

Rehabilitation for TB patients

Functional evaluation of patients and pulmonary rehabilitation

TB control programmes have prioritized early diagnosis and effective treatment of infectious cases to ensure rapid cure of individual patients and interruption of the transmission chain. Given most of the global TB burden is localized in countries with limited economic resources, the importance of investigating the functional status of the patients declared 'cured' to assess potential abnormalities and candidates for pulmonary rehabilitation has not gained much attention (Amaral et al., 2015; Muñoz-Torrico et al., 2016; Spruit et al., 2013).

With a main focus on chronic obstructive pulmonary disease (COPD), the American Thoracic Society/European Respiratory Society (ATS/ERS) rehabilitation guidelines indicate that rehabilitation is an effective intervention in chronic respiratory diseases, although TB is not individually mentioned. Recent evidence has shown that obstructive and/or restrictive functional sequelae may occur, potentially affecting quality of life (QoL) (Amaral et al., 2015; Muñoz-Torrico et al., 2016). Currently, no guidance on specific indications and procedures regarding the study and rehabilitation of TB sequelae is available (Amaral et al., 2015; Muñoz-Torrico et al., 2016), although TB rehabilitation was recently recommended in the ATS/ERS/Infectious Disease Society of America (IDSA)/Centers for Disease Control and Prevention (CDC) multidrug-resistant (MDR)-TB guidelines (Nahid et al., 2019).

The preliminary data available suggest that pulmonary rehabilitation is effective in patients with a previous history of TB and with impaired lung function. As more and more countries are potentially able to financially support rehabilitation for patients with post-TB sequelae, well-designed prospective studies are necessary to identify the individuals needing further assessment and to clarify which rehabilitation models can be implemented to ensure a functional recovery (Visca et al., 2019).

The evidence available on lung function impairment

A few studies have investigated mechanical lung function in TB patients. Already in 1961, Hallett and Martin described a 'diffuse obstructive pulmonary syndrome' among TB patients admitted to sanatoria (Hallett and Martin, 1961). Willcox and Ferguson (1989) identified airway obstruction in 68% of patients completing anti-TB treatment, with an inverse relationship between the extent of chest radiography lesions and forced expiratory volume in the first

second (FEV₁). Similarly, in South Africa, TB was found to be responsible for lung function impairment (Hnizdo et al., 2000). In a large population-based study involving 14 050 participants from 18 countries, a history of previous anti-TB treatment was associated with both airflow obstruction and spirometry restriction, and it was concluded that TB is a major cause of COPD in countries with a high TB prevalence (Amaral et al., 2015).

Worldwide, several studies have identified TB (treatment) as a positive predictor for loss of lung function. The conclusions of a South Korean study conducted between 2008 and 2012 recommended coupling regular lung function testing and smoking cessation as preventive measures for chronic airway obstruction (Jung et al., 2015). A study conducted in India in 2015 identified obstructive, restrictive, and mixed lung impairment disorders in TB patients after completing their treatment (Sailaja and Nagasreedhar, 2015). In China, treated TB was identified as an independent risk factor for airflow obstruction (Lam et al., 2010). In Papua New Guinea, effective management (early diagnosis and adequate treatment) of MDR-TB patients was considered essential to prevent post-treatment sequelae (Ralph et al., 2013).

Furthermore, a multicentre population-based study in Latin America involving over 5500 patients in five cities revealed that (self-reported) history of previous anti-TB treatment was significantly associated with airflow obstruction (Menezes et al., 2007). In Mexico, 70 patients cured of pulmonary TB were investigated, and frequent obstructive abnormalities were found, with impaired QoL (de la Mora et al., 2015). Last, in Texas, United States, pulmonary function was evaluated twice, after 20 weeks and at the end of anti-TB treatment, and TB treatment was identified as an independent risk factor for COPD, both in smokers and non-smokers (Vecino et al., 2011).

Therefore, it was recently suggested that lung function be assessed by performing spirometry, plethysmography, DLCO (diffusion for carbon oxide), arterial blood gas analyses, and evaluating the capacity to perform exercise via the 6-min walk test (6MWT). It is possible to describe the lesions with chest radiography and computed tomography before and after treatment. Clearly, the clinical assessment of infectious cases implies adequate infection control measures are in place (Migliori et al., 2019).

The evidence available on pulmonary rehabilitation

TB is clearly mentioned among the conditions for which pulmonary rehabilitation is useful according to the ATS/ERS guidelines and the South African COPD management guidelines (Spruit et al., 2013). In a recent study (Visca et al., 2019), pulmonary rehabilitation was effective in patients with a previous history of anti-TB treatment. Patients with impaired lung function reported a significant improvement in 6MWT, Borg dyspnoea and fatigue scores, FEV₁, forced vital capacity (FVC), mean arterial oxygen partial pressure (PaO₂), and median arterial blood oxygen saturation (SaO₂) (Visca et al., 2019).

In a recent editorial and in studies conducted in Benin, Zimbabwe, and Uganda (Chin et al., 2019; Fiogbe et al., 2019; Harries and Chakaya, 2019; Jones et al., 2017), the issue of the feasibility of post-treatment functional assessment of TB patients and subsequent pulmonary rehabilitation was discussed, with a focus on the perspective of low-income countries. In Uganda, a pulmonary rehabilitation package supervised by physiotherapists and requiring minimum equipment initiated at the health facility level, with aerobic and resistance exercises later managed at home, was demonstrated to be feasible and associated with clinically important improvements in QoL, exercise capacity, and respiratory outcomes (Jones et al., 2017).

A recent review (Hoger et al., 2014) recommended that future evaluation of post-treatment sequelae include the following (Figure 1): detailed information on patient characteristics (age, sex, ethnicity, etc.), TB disease (history of previous treatment, bacteriological status and pattern of drug resistance, previous drugs and regimens with adverse events), and pathophysiological status (spirometry with bronchodilator response), assessment of lung volumes (plethysmography), DLCO, arterial blood gases analysis, 6MWT, radiological evaluation, QoL evaluation, rationale and the features of the rehabilitation plan (with clear pre-/post-test comparisons), and a cost evaluation. Furthermore, studies should quantify the proportion of patients needing rehabilitation among those completing treatment. This will allow the need for pulmonary rehabilitation to be estimated and adequately planned at the programmatic level.

Optimized nutritional care for TB patients

The history of nutritional care

Nutritional care has been an important component of TB treatment throughout the history of European civilization. Lacking adequate drugs, Hippocrates' TB treatment consisted of resting, praying, drinking milk, exercise, and avoiding extreme weather conditions (Madkour et al., 2004). At the end of the nineteenth century, in the first sanatorium for TB patients, a more specific nutritional regimen was implemented in TB treatment. This diet was "a mix of meat with plenty of vegetables" (Kinghorn, 1921). Furthermore, to treat symptoms like night sweats, cognac was used (Kinghorn, 1921). In the first randomized trial testing the potential of streptomycin injections, the control standard of care consisted of nutrition and bed rest (Streptomycin in Tuberculosis Trials Committee, 1948). In 2013, the World Health Organization (WHO) published the first guidelines on nutritional care and support specifically for patients with TB. In these guidelines, the WHO stressed that all patients with active TB are entitled to individualized nutritional assessment and management, including counselling and therapy (World Health Organization, 2013).

Malnutrition and its implications for TB

Malnutrition is defined by the European Society for Clinical Nutrition and Metabolism (ESPEN) as "a state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat-free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease" (Cederholm et al., 2017). In general, malnutrition is reported to have a huge impact on patient outcomes and healthcare costs (Muscaritoli et al., 2017). Disease-related malnutrition is characterized by a loss of fat-free mass; therefore, normal weight, overweight, and obese patients with TB can be malnourished (Paton et al., 2004). This implies a decline in muscle function, which leads to dependency and less participation in society for the patient. Regaining physical function shortens the time needed for recovery and enables patients with TB to resume work (Cederholm et al., 2017; Paton et al., 2004). The prevalence of malnutrition in patients with TB is calculated to be 70%, and in this population, malnutrition is associated with a two-fold higher risk of dying from TB (Bhargava et al., 2013).

Malnutrition is considered an important potentially reversible risk factor for TB treatment failure (Choi et al., 2017b). It is hypothesized that pharmacokinetic variability, resulting from changes in malabsorption (Montalto et al., 2008), can influence efficacy. Patients with TB may suffer from malabsorption because of malnutrition, which can be increased by possible comorbidities such as diabetes and HIV/AIDS. Subsequently, decreased absorption of anti-TB drugs is likely to result in low drug exposure. This may lead to unfavourable outcomes by treatment failure and the development of drug resistance (Ter Beek et al., 2019).

Nutritional assessment, therapy, and monitoring

Malnutrition is not disease-specific but is a 'nutrition disorder' (Cederholm et al., 2017). As low body mass index (BMI) is a hallmark of chronic malnutrition that involves the loss of both fat and muscle tissue, a BMI < 18.5 kg/m² may be used as a measure for general public health purposes (Cederholm et al., 2015). However, in clinical practice, using BMI exclusively is of less relevance for nutritional assessment, since in disease-related malnutrition,

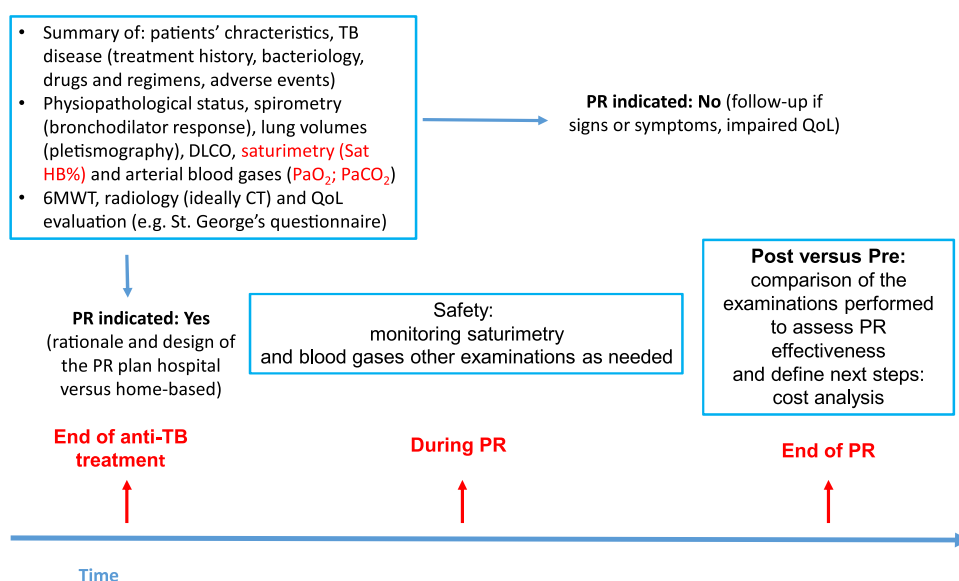


Figure 1. Summary of the core interventions at the end of anti-tuberculosis treatment and during pulmonary rehabilitation.

DLCO: diffusing capacity of the lung for carbon monoxide; Sat HB%: haemoglobin saturation as a percentage; PaO₂/PaCO₂: arterial blood tension of oxygen and carbon dioxide; 6MWT: 6-min walking test; CT: computed tomography; QoL: quality of life; PR: pulmonary rehabilitation.

in situ immune response – granuloma

systemic immune responses, lymph nodes

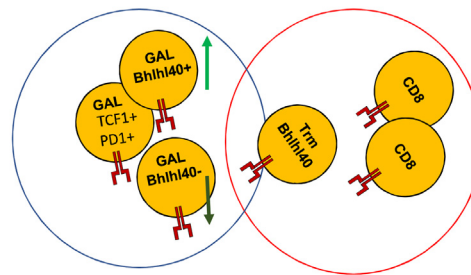


Figure 2. Immune responses in *Mycobacterium tuberculosis* infection. Tissue resident T-cells (Trm) and tumour infiltrating T-cells (TIL) exhibit increased Bhlh40 expression; however, this is not the case for peripheral (CD8+) T-cells. GAL (granuloma-associated lymphocytes; Tully et al; 2005) correspond to TIL. Increased Bhlh40 is associated with increased immune effector functions, increased 'mitochondrial fitness', and increased competence to contain pathogens or transformed cells (light green arrow). In contrast, decreased Bhlh40 expression is linked with loss of immune competence (dark green arrow). Immune cells may be recruited into the granuloma via Trm resources, from the peripheral circulation, or from lymph nodes. TCF1+ PD1+ T-cells have stem-like properties and are crucial in long-term immune memory. Antigen-specific CD8+ T-cells are vital for immune surveillance, but may also be responsible for mediating cachexia.

muscle mass is mainly lost (Cederholm et al., 2015). A gold standard for malnutrition is not available, which complicates consensus on how nutritional assessment and its validation should be conducted. However, in 2018, consensus diagnostic criteria for malnutrition were published by ESPEN and the American Society for Parenteral and Enteral Nutrition (ASPEN) to accommodate uniformity in nutritional assessment, i.e. the 'GLIM criteria' (Global Leadership Initiative on Malnutrition) (Cederholm et al., 2019). These criteria are both phenotypic (weight loss, low BMI, reduced muscle mass) and aetiological (reduced food intake or assimilation, disease burden/inflammatory condition), and are preceded by validated screening for malnutrition risk (Cederholm et al., 2019).

After diagnosing malnutrition, an individualized treatment plan needs to be developed. This tailored treatment plan needs to be based on sufficient proteins (and distribution) and energy from either regular foods or medical nutritional supplements if necessary, and preferably in combination with training (Ockenga et al., 2006). The nutritional counselling and measurements that are performed to assess malnutrition should be repeated regularly during the treatment and (pulmonary) rehabilitation period, to allow adjustment of the nutritional treatment plan if necessary.

New insights from protective immune responses—cross-fertilizing concepts for anti-MTB immune surveillance

New insights from cancer research and biological therapy are guiding innovative immunological therapies targeted against defined molecular targets. A novel pathway has been suggested on how disease-related malnutrition is mediated, and is a common finding in TB patients. Nutritional status is a key factor in shaping immune responses. Under normal circumstances, most immune cells use a glucose-based mechanism to generate energy. In nutrient-deficient states, alternative sources are used to generate energy, such as proteins and fatty acids. Baazim et al. showed that infection-induced cachexia is not only mediated by tumour necrosis factor alpha (TNF- α), interleukin (IL)-1 β , and IL-6 leading to proteolysis and lipolysis, but also by antigen-specific CD8+ T-cells that mediate cachexia by adipose tissue remodelling (Baazim et al., 2019) (Figure 2). Furthermore, the containment of tissue infections requires the involvement of tissue resident immune cells (Trm cells). These cells are enriched in the lung and are thought to mediate an important line of defence against invading pathogens (Behr et al., 2018). Bhlh40 is a key factor mediating containment of infectious pathogens (or transformed cells) (Li et al., 2019). Mice with reduced Bhlh40 cells exhibit reduced survival in influenza-positive animals; increased Bhlh40

expression results in increased interferon-gamma production in the Th1 compartment. These may be promising clinically relevant markers to identify individuals who may benefit from immunomodulatory strategies targeting the biological pathways associated with long-term protective immune responses.

Conclusions

In this review on the holistic approach to TB patients, we have discussed the recent evidence on the importance of evaluating functional status at the completion of treatment in order to identify candidates for pulmonary rehabilitation. We have shown that pulmonary rehabilitation is effective in improving functional parameters, the capacity to perform exercise (walking test), and quality of life. We have described the recent evidence and implications at the immunological level, identifying priorities for future research. We have also discussed the damage produced by malnutrition and the importance of assessing the nutritional status. The importance of addressing malnutrition correctly and in a timely fashion is essential in reducing morbidity and mortality.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval

Approval was not required.

Conflict of interest

No competing interest declared.

Acknowledgements

This article is part of the activities of the Global Tuberculosis Network (GTN; Committees on TB Treatment, Working Group on Pulmonary Rehabilitation, and Global TB Consilium) and of the WHO Collaborating Centre for Tuberculosis and Lung Diseases, Tradata, ITA-80, 2017–2020-GBM/RC/LDA. This article is part of a supplement entitled *Commemorating World Tuberculosis Day March 24th, 2020: "IT'S TIME TO FIND, TREAT ALL and END TUBERCULOSIS!"* published with support from an unrestricted educational grant from QIAGEN Sciences Inc.

References

- Amaral AF, Coton S, Kato B, Tan WC, Studnicka M, Janson C, et al. Tuberculosis associates with both airflow obstruction and low lung function: BOLD results. *Eur Respir J* 2015;46:1104–12, doi:http://dx.doi.org/10.1183/13993003.02325-2014.
- Baazim H, Schweiger M, Moschinger M, Xu H, Scherer T, Popa A, et al. CD8(+) T cells induce cachexia during chronic viral infection. *Nat Immunol* 2019;20(6):701–10, doi:http://dx.doi.org/10.1038/s41590-019-0397-y.
- Behr FM, Chuwonpad A, Stark R, van Gisbergen K. Armed and ready: transcriptional regulation of tissue-resident memory CD8 T cells. *Front Immunol* 2018;9:1770, doi:http://dx.doi.org/10.3389/fimmu.2018.01770.
- Bhargava A, Chatterjee M, Jain Y, Chatterjee B, Kataria A, Bhargava M, et al. Nutritional status of adult patients with pulmonary tuberculosis in rural central India and its association with mortality. *PLoS One* 2013;8(10):e77979, doi:http://dx.doi.org/10.1371/journal.pone.0077979.
- Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. *Clin Nutr* 2017;36:49–64, doi:http://dx.doi.org/10.1016/j.clnu.2016.09.004.
- Cederholm T, Bosaeus I, Barazzoni R, Bauer J, Van Gossum A, Klek S, et al. Diagnostic criteria for malnutrition—an ESPEN consensus statement. *Clin Nutr* 2015;34:335–40, doi:http://dx.doi.org/10.1016/j.clnu.2015.03.001.
- Cederholm T, Jensen GL, Correia MITD, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition—a consensus report from the global clinical nutrition community. *J Cachexia Sarcopenia Muscle* 2019;10:207–17, doi:http://dx.doi.org/10.1002/jcsm.12383.
- Chin AT, Rylance J, Makumbirofa S, Meffert S, Vu T, Clayton J, et al. Chronic lung disease in adult recurrent tuberculosis survivors in Zimbabwe: a cohort study. *Int J Tuberc Lung Dis* 2019;23:203–11, doi:http://dx.doi.org/10.5588/ijtld.18.0313.
- Choi C-J, Choi W-S, Kim C-M, Lee S-Y, Kim K-S. Risk of sarcopenia and osteoporosis in male tuberculosis survivors: Korea National Health and Nutrition Examination Survey. *Sci Rep* 2017a;7(1), doi:http://dx.doi.org/10.1038/s41598-017-12419-y 13127 13127.
- Choi R, Jeong BH, Koh WJ, Lee SY. Recommendations for optimizing tuberculosis treatment: therapeutic drug monitoring, pharmacogenetics, and nutritional status considerations. *Ann Lab Med* 2017b;37:97–107, doi:http://dx.doi.org/10.3343/alm.2017.37.2.97.
- de la Mora IL, Martínez-Oceguera D, Laniado-Laborín R. Chronic airway obstruction after successful treatment of tuberculosis and its impact on quality of life. *Int J Tuberc Lung Dis* 2015;19(7):808–10, doi:http://dx.doi.org/10.5588/ijtld.14.0983.
- Fiogbe AA, Agodokpessi G, Tessier JF, Affolabi D, Zannou DM, Adé G, et al. Prevalence of lung function impairment in cured pulmonary tuberculosis patients in Cotonou, Benin. *Int J Tuberc Lung Dis* 2019;23:195–202, doi:http://dx.doi.org/10.5588/ijtld.18.0234.
- Hallett WY, Martin CJ. The diffuse obstructive pulmonary syndrome in a tuberculosis sanatorium. I. Etiologic factors. *Ann Intern Med* 1961;54:1146–55.
- Harries AD, Chakaya JM. Assessing and managing pulmonary impairment in those who have completed TB treatment in programmatic settings. *Int J Tuberc Lung Dis* 2019;23(9):1044–5, doi:http://dx.doi.org/10.5588/ijtld.19.0168.
- Hnizdo E, Singh T, Churchyard G. Chronic pulmonary function impairment caused by initial and recurrent pulmonary tuberculosis following treatment. *Thorax* 2000;55(1):32–8.
- Hoger S, Lykens K, Beavers SF, Katz D, Miller TL. Longevity loss among cured tuberculosis patients and the potential value of prevention. *Int J Tuberc Lung Dis* 2014;18(11):1347–52, doi:http://dx.doi.org/10.5588/ijtld.14.0242.
- Jones R, Kirenga BJ, Katagira W, et al. A pre-post intervention study of pulmonary rehabilitation for adults with post-tuberculosis lung disease in Uganda. *Int J Chronic Obstruct Pulmon Dis* 2017;12:3533–9, doi:http://dx.doi.org/10.2147/COPD.S146659.
- Jung JW, Choi JC, Shin JW, Kim JY, Choi BW, Park IW. Pulmonary impairment in tuberculosis survivors: the Korean National Health and Nutrition Examination Survey 2008–2012. *PLoS One* 2015;10(10):e0141230, doi:http://dx.doi.org/10.1371/journal.pone.0141230.
- Kinghorn HM, Hermann Brehmer. *Trans Am Climatol Clin Assoc* 1921;37:193–210.
- Lam KB, Jiang CQ, Jordan RE, Miller MR, Zhang WS, Cheng KK, et al. Prior TB, smoking, and airflow obstruction: a cross-sectional analysis of the Guangzhou Biobank Cohort Study. *Chest* 2010;137(3):593–600, doi:http://dx.doi.org/10.1378/chest.09-1435.
- Li C, Zhu B, Son YM, Wang Z, Jiang L, Xiang M, et al. The transcription factor Bhlhe40 programs mitochondrial regulation of resident CD8(+) T cell fitness and functionality. *Immunity* 2019;51(3):491–507 e7, doi:http://dx.doi.org/10.1016/j.immuni.2019.08.013.
- Madkour MM, Al-Otaibi KE, Al-Swailem R. The evolution of tuberculosis treatment. In: Madkour MM, editor. *Tuberculosis*. Berlin Heidelberg: Springer; 2004 p. 25.
- Menezes AM, Hallal PC, Perez-Padilla R, Jardim JR, Muñio A, Lopez MV, et al. Tuberculosis and airflow obstruction: evidence from the PLATINO study in Latin America. *Eur Respir J* 2007;30(6):1180–5.
- Migliori GB, Nardell E, Yedilbayev A, D'Ambrosio L, Centis R, Tadolini M, et al. Reducing tuberculosis transmission: a consensus document from the World Health Organization Regional Office for Europe. *Eur Respir J* 2019;53(6), doi:http://dx.doi.org/10.1183/13993003.00391-2019 pii: 1900391.
- Montalto M, Santoro L, D'Onofrio F, Curigliano V, Gallo A, Visca D, et al. Adverse reactions to food: allergies and intolerances. *Dig Dis* 2008;26(2):96–103, doi:http://dx.doi.org/10.1159/000116766.
- Muñoz-Torrico M, Rendon A, Centis R, D'Ambrosio L, Fuentes Z, Torres-Duque C, et al. Is there a rationale for pulmonary rehabilitation following successful chemotherapy for tuberculosis? *J Bras Pneumol* 2016;42(5):374–85, doi:http://dx.doi.org/10.1590/S1806-37562016000000226.
- Muscaritoli M, Krznaric Z, Barazzoni R, Cederholm T, Golay A, Van Gossum A, et al. Effectiveness and efficacy of nutritional therapy—a cochrane systematic review. *Clin Nutr* 2017;36(4):939–57, doi:http://dx.doi.org/10.1016/j.clnu.2016.06.022.
- Nahid P, Mase SR, Migliori GB, Sotgiu G, Bothamley GH, Brozek JL, et al. Treatment of drug-resistant tuberculosis. An official ATS/CDC/ERS/IDSA clinical practice guideline. *Am J Respir Crit Care Med* 2019;200(10):e93–e142, doi:http://dx.doi.org/10.1164/rccm.201909-1874ST.
- Ockenga J, Grimble R, Jonkers-Schuitema C, Macallan D, Melchior JC, Sauerwein HP, et al. DGE (German Society for Nutritional Medicine), Suttman U, ESPEN (European Society for Parenteral and Enteral Nutrition). ESPEN guidelines on enteral nutrition: wasting in HIV and other chronic infectious diseases. *Clin Nutr* 2006;25:319–29.
- Paton NI, Chua YK, Earnest A, Chee CB. Randomized controlled trial of nutritional supplementation in patients with newly diagnosed tuberculosis and wasting. *Am J Clin Nutr* 2004;80:460–5.
- Ralph AP, Kenangalem E, Waramori G, Pontororing GJ, Sandjaja, Tjitra E, et al. High morbidity during treatment and residual pulmonary disability in pulmonary tuberculosis: under-recognised phenomena. *PLoS One* 2013;8(11):e80302, doi:http://dx.doi.org/10.1371/journal.pone.0080302.
- Sailaja K, Nagasreedhar Rao H. Study of pulmonary function impairment by spirometry in post pulmonary tuberculosis. *J Evol Med Dent Sci* 2015;4(42):7365–70, doi:http://dx.doi.org/10.14260/jemds/2015/1068.
- Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nicl L, Rochester C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med* 2013;188(8):e13–64, doi:http://dx.doi.org/10.1164/rccm.201309-1634ST.
- Streptomycin in Tuberculosis Trials Committee. Streptomycin treatment of pulmonary tuberculosis. A Medical Research Council Investigation. *Br Med J* 1948;2:769–82, doi:http://dx.doi.org/10.1136/bmj.2.4582.769.
- Ter Beek L, Alffenaar JC, Bolhuis MS, van der Werf TS, Akkerman OW. Tuberculosis-related malnutrition: public health implications. *J Infect Dis* 2019;220:340–1, doi:http://dx.doi.org/10.1093/infdis/jiz091.
- Vecino M, Pasipanodya JG, Slocum P, Bae S, Munguia G, Miller T, et al. Evidence for chronic lung impairment in patients treated for pulmonary tuberculosis. *J Infect Public Health* 2011;4(5–6):244–52, doi:http://dx.doi.org/10.1016/j.jiph.2011.08.005.
- Visca D, Zampogna E, Sotgiu G, Centis R, Sadari L, D'Ambrosio L, et al. Pulmonary rehabilitation is effective in patients with tuberculosis pulmonary sequelae. *Eur Respir J* 2019;53(3), doi:http://dx.doi.org/10.1183/13993003.02184-2018 pii: 1802184.
- Willcox PA, Ferguson AD. Chronic obstructive airways disease following treated pulmonary tuberculosis. *Respir Med* 1989;83(3):195–8.
- World Health Organization. Nutritional care and support for patients with tuberculosis guideline. Geneva: WHO; 2013. https://www.who.int/tb/publications/nutcare_support_patients_with_tb/en/.